12 Overview and commentary on the Efficacy and Safety evidence

1 OVERVIEW AND COMMENTARY ON THE EFFICACY DATA

12.1.1 Design and methods in 8 largest placebo-controlled IC trials

Walking tests were conducted in stable claudicants with PAD in these 8 placebo-controlled, randomized, parallel-group trials.[41] In an attempt to demonstrate efficacy the claudication-limited walking distance (total distance (ACD), and/or distance at claudication onset (ICD) was measured during treadmill testing.

There was a range of pre-treatment walking tolerance, walking test methodology and treatment durations in these trials. A summary of these characteristics (as well as sample sizes, doses, and other baseline characteristics) is shown below:

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[41] as well as in 4 smaller such trials not pooled here.

Table: 57
Methods and baseline characteristics
in the 8 largest placebo-controlled intermittent claudication trials

	study 21-92-202	study 21-96-202	study 21-94-201	study 21-94-301	study 21-94-203	study 21-95-201	Study 21-93-201	study 21-90-201
ALL GROUPS: Randomized: to clz or placebo[42]	n=516	n=467	n= 394	n=247	n=239	n=215	n=189	n=81
to CLZ 50 mg bid	n=175	0	n=132	0	0	0	0	0
to CLZ 100 mg bid	n=171	n=228	n=133	n=123	n=119	n=72	n=95	n=54
to CLZ 150 mg bid	0	0	0	0	0	n=73	0	0
to Placebo	n=170	n=239	n=129	n=124	n=120	n=70	n=94	n=27
to pentoxifylline	0	n=232	0	n=123	0	0	0	0
METHODS: treatment duration	24 wks	24 wks	24 wks	24 wks	16 wks	12 wks	12 wks	16 wks
treadmill speed	3.2 km/h	3.2 km/h	3.2 km/h	3.2 km/h	3.2 km/h	3.2 km/h	3.2 km/h	3.2 km/h
treadmill incline	immediate; 12. 5%	delayed; 0% start, then 3.5% increase ea. 3 min	immediate; 12. 5%	immediate; 10%	delayed; 0% start, then 3.5% increase ea. 3 min	immed-iate; 12. 5%	Delayed; 0% start, then 3.5% increase ea. 3 min	immed-iate; 12. 5%
COVARIATES[43] mean age	65 yr	66 yr	64 yr	66 yr	65 yr	66 yr	67 yr	67 yr
mean extent of male majority	76%	76%	76%	72%	76%	79%	84%	80%
mean extent of Caucasian majority	88%	89%	86%	99.5%	87%	87%	85%	99%
mean pre-treatment resting trough ABI	0.62	0.67	0.64	0.62	0.66	0.64	0.66	0.57
mean pre-treatment trough ACD	137 m	237 m	120 m	131 m	240 m	123 m	279 m	152 m

Each of the above was a randomized, double-blind trial.

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me studies (96-202 and 94-301) had additional subjects randomized to a positive-control arm, as shown elsewhere in the table.

[43] pooling all clz groups and the placebo group.

The populations studied were generally representative of the published experience with intermittent claudication populations. In the sponsor's analysis of ten published articles[44] (including a total of 2,789 patients), as in this NDA database, patients were generally male (81%) with average age of 62 years, with a majority having a history of smoking, and a minority being diabetic.

12.1.2   Tests stopped for nonspecific reasons   ^

In a discrete fraction of pooled subjects, the tests were stopped for reasons other than claudication. This occurred in 20% of subjects randomized to clz 100 mg bid vs 14% of placebo-randomized subjects (as well as in 29%, and 15% of subjects randomized to clz 150 mg bid, and 50 mg bid, respectively). Nonspecific reasons for stopping including dyspnea, general fatigue, leg fatigue without pain, back or joint pain.

12.1.3   Effect to increase ACD   ^

Summaries ACD results, pooling the 8 largest placebo-controlled IC trials, are shown below. Shown in the next table are efficacy results at the end of the final treatment week. Missing data were handled by the LOCF method. Sample sizes are the numbers of CLZ subjects included in each efficacy analysis; roughly comparable numbers received placebo. Two studies (96-202 & 94-301) had additional subjects randomized to pentoxifylline. Raw median results are based on the FDA statisticians' analyses, means are based on sponsor's analyses.

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[44] the basis by which these were selected is unclear.

Table: 58

Overview of change from pre-treatment ACD, at trough
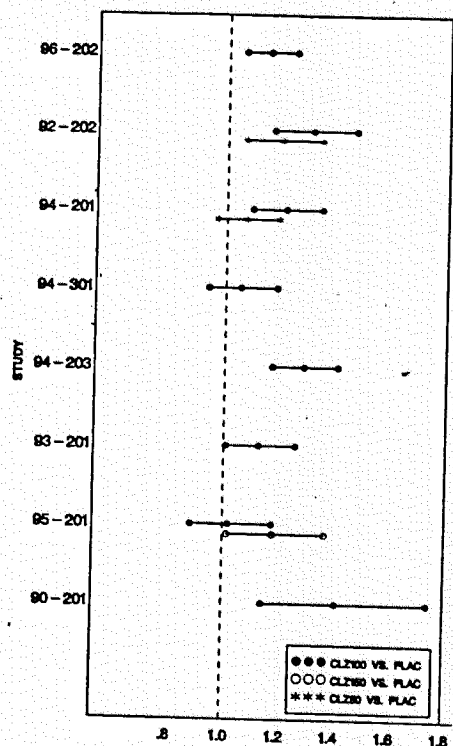### (in the 8 largest placebo-controlled trials; LOCF)

	study 21-92-202	study 21-94-201	study 21-90-201	Study 21-95-201	study 21-94-301	study 21-96-202	study 21-94-203	study 21-93-201
METHODS: treatment duration	24 wks	24 wks	16 wks	12 wks	24 wks	24 wks	16 wks	12 wks
treadmill incline	immediate; 12.5%				immediate; 10%	delayed; 0% start, then 3.5% increase every 3 min		
CLZ 50 mg bid sample size	n=139	n=128	--	--	--	--	--	--
placebo-corrected MEDIAN change	18 m	7.5 m	--	--	--	--	--	--
placebo-corrected MEAN change	37.7 m	21 m	--	--	--	--	--	--
log transformed ratio clz:plac	1.20	1.08	--	--	--	--	--	--
CLZ 100 mg bid sample size	n=140	n=124	n=54	n=60	n=123	n=205	n=108	n=86
placebo-corrected MEDIAN change	25.5 m	17.5 m	26.5 m	-6.5 m	8 m	24 m	61.5 m	30.5 m
placebo-corrected MEAN change	106.2 m	58.6 m	105.8 m	-1.6 m	33.6 m	42.6 m	72 m	37.9 m
log transformed ratio clz:plac	1.32	1.22	1.45	1.01	1.05	1.14	1.31	1.16
CLZ 150 mg bid sample size	--	--	--	n=53	--	--	--	--
placebo-corrected MEDIAN change	--	--	--	19.5 m	--	--	--	--
placebo-corrected MEAN change	--	--	--	44.2 m	--	--	--	--
log transformed ratio clz:plac	--	--	--	--	--	--	--	--

Therapeutic effect remained observable, irrespective of the means of handling of missing data. This is demonstrated by the following two figure, the first of which presents the ACD results after ~ploying the pre-specified LOCF method of carrying foward nonmissing data, and the second of .ich shows results (retrospectively analyzed) when no data imputation was applied to cases of missing data.

Figure: 23

Log transformed ratio (clz:placebo) of estimated treatment effect to change pre-treatment ACD:

(ITT datasets; 8 largest placebo trials)

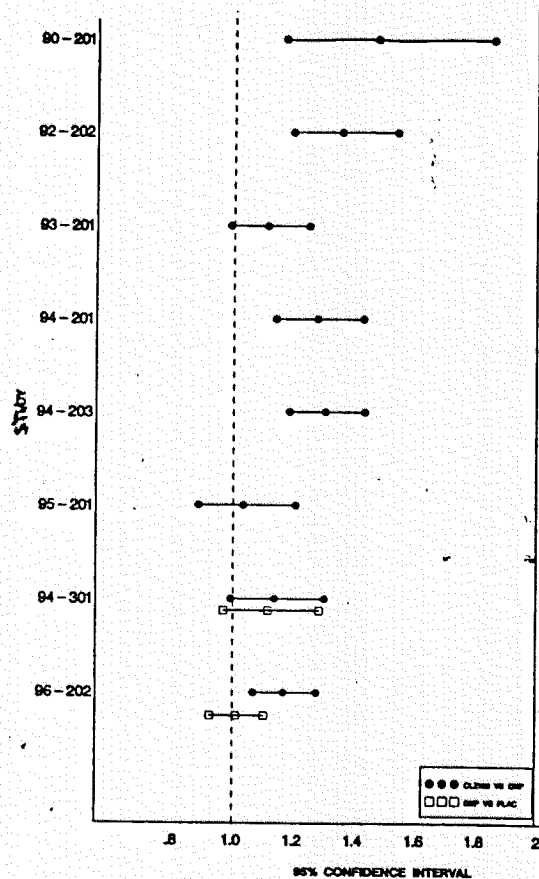**Method of missing data handling: LCOF**

[source: modified photocopy of figure 4.2-1, submission 6/1/98]

Shown above are point estimates of effect and 95% CI.

Figure: 24
Log transformed ratio (clz 100 mg bid:placebo) of
estimated treatment effect to change pre-treatment ACD:
(ITT datasets; 8 largest placebo trials)

Method of missing data handling: no imputation (observed cases)

[source: modified photocopy of pg 126, submission #36, 5/22/98]

Shown above are point estimates of effect and 95% CI.

12.1.4 Apparent time-course of ACD effect: ^

∍ time-course of the ACD-increasing effect is somewhat difficult to extract from the submitted
_a, for several reasons: alpha was spent entirely on results obtained at end-study (12-24 weeks)
so there is limited statistical certainty to findings obtained earlier in the studies; LOCF imputation
(applied in substantial numbers of dropouts) distorted the temporal course of therapeutic effect,
and the best described time-course data were based on mean results which provide only a low
fidelity description for skewed data such as these. Within these constraints only a crude
description can be generated from the mean time-course presented above in the individual study
sections: there it roughly appears that effect onsets by approximately 8-16 weeks.

12.1.5   Across-study comparisons of results: ^

Between the 8 largest placebo studies there were variable degrees of imposition of a treadmill
incline upon walking subjects. While the treadmills in all 8 of these studies employed a uniform
speed of 3.2 km/h (i.e. 53.3 m/min), in some studies the tests were conducted at an immediate
_(and constant) incline of 12.5%, whereas in others there was a delayed and incremental incline
(after starting at zero, the incline increased only gradually by 3.5% every 3 minutes). The studies
which employed the "delayed incline" protocol would have been expected (given all else being
equal) to produce larger ACDs than in studies using "immediate-incline" protocols[45]. Placebo
ients were present with which to normalize the data, but this would not provide correction per
∪∪ for any biological interaction which may have existed between CLZ effect and incline load..

Among the 4 studies that employed the same "immediate-12.5% incline" walking protocol, two of
the three longer duration (16-24 week) ones (specifically, studies 21-92-202, and 21-90-201)
showed reasonable concordance with respect to the point estimated raw effect of 100 mg bid CLZ
to change pre-treatment ACD at trough (i.e. the median, placebo-corrected changes were 25.5 and
26.5 meters, respectively)[46]. The third "immediate-12.5% incline", longer duration trial (i.e.
study 21-94-201) showed a smaller trough effect of 100 mg bid CLZ on ACD (a median, placebo-
corrected change of 17.5 meters). The reason for this is not known with certainty, but there are
plausible explanatory factors:

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[45] In "immediate-incline" protocols a walker reaches, say 160 m (this distance marks the end of the initial no-load
phase of the "delayed-incline" protocols) only after continually working against an incline (which was usually
pitched at 12.5%). Another walker with functionally equivalent peripheral arterial disease, if tested instead with
the "delayed-incline" treadmill protocol, would face no incline workload while travelling this 160 m. Not until
640 m of walking (i.e. at the end of 12 minutes) would the instantaneous (as opposed to cumulative) burden of
∽admill incline even begin to become greater for the "delayed-incline" walker (wherein he would just begin to
∍ a 14% incline) than for the "immediate-incline" walker.
[—] this is not to say that the smaller and early-terminated study 21-90-201 is similarly compelling, but just that it
tends to support the results of the larger study.

a. in study 21-94-201 the walking tests were, in CLZ 100 mg bid-randomized subjects, more frequently stopped for nonspecific reasons prior to the manifestation of distance-limiting claudication (23% of the time) than they were so stopped in placebo-randomized subjects (14%). This plausibly contributes to an underestimation of the size of the ACD-increasing effect of CLZ, relative to that of placebo.

b. in study 21-94-201 there were disproportionately more dropouts in the high dose CLZ group (29%, vs 17% in the placebo group). Since it appears that the onset of a significant ACD-improving effect of CLZ is delayed, relative to the onset of significant adverse effects, the carried-foward ACD values (from the CLZ group's early dropouts) would tend to be unreflective of the eventual therapeutic response. This would tend to distort towards underestimation the late-in-study, LOCF-based effect estimates.

In the remaining study which used this "immediate-12.5% incline" treadmill protocol (i.e. study 21-95-201) there was essentially no median effect of 100 mg bid CLZ on ACD at 12 weeks. The reason for this may have a basis in certain identifiable variables[47]:

a. in study 21-95-201 there was a modestly greater frequency of stopping of tests prior to claudication becoming exercise-ceasing among CLZ 100 mg bid-randomized subjects (20%), relative to placebo subjects (15%).

in study 21-95-201 there was a relatively brief (12 week) exposure duration.[48]

c. if valid to assume that the significant treatment-by-baseline interaction found in the better-powered study 21-92-202 is an accurate general description of CLZ's actions,[49] then the relatively severe degree of claudication in study 21-95-201's population (mean baseline ACD of 123 m) could contribute to the lesser effect.[50]

The one study which employed an "immediate-incline" walking protocol (study 21-94-301) at a lesser degree of pitch (i.e. 10%) showed essentially no median effect on ACD at 24 weeks. The reason for this is not clear. It is noted that walking tests in this study were, in CLZ-randomized subjects, somewhat more frequently stopped for nonspecific reasons prior to the manifestation of distance-limiting claudication (19% of the time) than they were so stopped in placebo-randomized subjects (12%). This plausibly contributed (albeit modestly) to a degree of underestimation of the size of the ACD-increasing effect of CLZ, relative to that of placebo.

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[47] so too these factors could account for the limited effect of 150 mg bid CLZ in this study.

[48] the exposure duration variable does not seem to be sufficiently explanatory, insofar as at roughly this timepoint, this dose showed a numerically larger-to-considerably larger mean effect in other "immediate-12.5% incline" studies (i.e. 21-92-202, 21-94-201, and 21-90-201).

[49] study 92-202, the effect on ACD was lesser in those with smaller pre-treatment ACD.

[50] this would not be a sufficient explanation insofar as "immediate-12.5% incline" studies 21-94-201, and 21-90-201 showed a greater efficacy at 12 weeks, despite similarly "sick" populations.

The 3 studies which employed the same "delayed-incremental incline" walking protocol (i.e. dies 21-96-202, 21-94-203, and 21-93-201) would have been expected (all else being sumed to be equal) to be biased towards overestimating ACD, relative to the results obtained with "immediate-incline" protocols. In fact, 2 of these 3 studies did find larger median changes from pre-treatment ACD than those found in the "immediate(12.5%)-incline" treadmill studies. Study 21-96-202 was the only exception. The reason for this is not clear, but may have a basis in certain identifiable variables:

a. there was a greater frequency among CLZ 100 mg bid-randomized subjects (25%), relative to placebo subjects (15%), of stopping of tests prior to actual manifestation of distance-limiting claudication.

b. there was relatively large pre-treatment ACD (the mean was about 100 m larger than in study 21-92-202), and this may have perhaps exerted some efficacy-limiting influence.

12.1.6   Peak vs trough results   ∧

The findings at presumed peak were explored in only 2 of the 8 largest placebo-controlled trials. In study 21-93-201, at trough on week 12 the clz group's ACD showed a 13% geometric mean change from the baseline ratio (clz:placebo), while an 18% geometric mean change was demonstrated at presumed peak. The raw results were a 38 meter *mean* placebo-corrected change rough, vs about a 50 meter *mean* placebo-corrected change at presumed peak (the placebo-corrected *median* changes were 30.5 meter at trough vs 49 meter at presumed peak).

In contrast, in study 21-94-203 the estimated CLZ effect on ACD at presumed peak (3-4 hours after dosing) was less than the estimated effect at trough, i.e. the week 16 ratio (cilostazol: placebo) of geometric mean change from pre-treatment ACD was approximately 20% at presumed peak vs about 29% at trough (the raw, placebo-corrected *median* changes were 61.5 meter at trough vs 42 meter at presumed peak). The reason for this is unclear: perhaps 3-4 hours post-dosing did not represent the actual pharmacodynamic peak.

12.1.7   Efficacy in demographic subgroups   ∧

Pooled demographic subgroup comparisons were described by the sponsor as follows[51]: using the log-transformed ITT/LOCF analysis pooling across the 8 largest placebo-controlled trials, they reported that subjects in the 100 mg bid and 50 mg bid clz groups had greater improvements in ACD at the end of treatment, relative to placebo, irrespective of gender, age (age ≥65 years compared to age > 65), race (comparing Caucasian to non-Caucasian), smoking status, use of bet blockers or calcium-channel blockers, diabetes, duration of disease, or hypertension. . .

1.8   Pentoxifylline comparisons: ∧

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[51] in their 6/1/98 submission (Advisory Committee briefing package).

In study 21-96-202 the point-estimated ratio of relative effect size was a statistically significant ˙ '6 (CLZ : PTX). However, this finding was not replicated by study 21-94-301; there CLZ was . statistically distinguishable from OXP.

12.2   OVERVIEW AND COMMENTARY ON THE SAFETY DATA

For a comprehensive description of safety results see the above safety section of this review. Major issues are extracted here.

12.2.1   Deaths

Subjects with confounding reasons for walking intolerance were excluded, and although this strengthened the validity of the anti-claudication claim it also likely resulted in a lowering of the number of fatal events. With relatively few fatal events the derived estimates of mortality were rendered highly variant. Thus the available data provide no useful basis by which to exclude a risk of death on the order of that seen in CHF patients using other drugs in the PDE III inhibitor class (i.e. a relative risk of around 1.3).

Oral milrinone, in the PROMISE trial, caused a 28% mean increase in all-cause mortality (95% 1-61%), and a 34% increase in cardiovascular mortality (95% CI, 6-69%) among NYHA class ---IV CHF patients exposed to a background of diruetics, digoxin, and an ACE inhibitor. Dr. Milton Packer, the principal investigator of that trial, reports[52] that the majority of excess deaths were attributed (albeit by an unvalidated classification scheme) to sudden death, and that no other serious AE were in excess among milrinone-treated patients. The latter finding makes doubtful the prospect of increasing the power of any future CLZ survival trial by means of utilizing a composite endpoint.

12.2.2   Arrhythmogenicity

The sponsor's reliance on only a small number of ambulatory EKG observations limited the power of the above described analysis to detect any electrocardiographic evidence of CLZ-mediated cardiac ectopy. Nonetheless, is clear that in the 8 largest placebo-controlled studies palpitations occurred commonly, in a dose-related fashion, and with sufficient severity to cause dropping in 1% of the clz 200 mg/d group (compared to 0.1% of the placebo group).

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[52]via personal communication on 7/23/98.

12.2.3 AE-associated dropouts

The rates of dropping out for headache, diarrhea, and palpitation were dose-related. Headache-associated dropout occurred at rates of 1.3%, 3.7%, and 6.8%, respectively in the low, medium and high dose cilostazol groups, while at a 0.3% rate in the placebo group. Diarrhea-associated dropout occurred at rates of 0.3%, 0.8, and 6.8% respectively in the low, medium and high dose cilostazol groups, while at a 0.4% rate in the placebo group.

12.2.4 Bleeding risk

Japan's labelling reportedly contraindicates CLZ's use in patients with known hemorrhage, and cautions about concomitant use of warfarin or ticlopidine. There were apparently drug-related deaths from gastric hemorrhage in the setting of concomitant use of these agents. Additionally, among 2789 patients exposed to CLZ in Asian post-marketing studies there were 3 events of retinal hemorrhage.

In this NDA there were 4 reported cases of serious bleeding among CLZ-randomized subjects:

a. bleeding after ruptured aortic aneurysm: the underlying vasculopathic event is plausibly a sufficient cause for the major bleed which resulted, although a contributory role (albeit perhaps minor) of CLZ's antiplatelet activity cannot be excluded.

b. lower GI hemorrhage: the degree to which CLZ interacted with the underlying diverticulosis is not readily dissected from the available data.

c. hematuria: the underlying post-radiation hemorrhagic cystitis is conceivably a sufficient cause for this case of bleeding.

d. retroperitoneal bleed: the warfarin, urokinase, and aspirin administration just prior to this bleed is presumably of major etiologic significance, and plausibly of sole significance given that CLZ had been discontinued for over 4 elimination half-lives.

Conclusions regarding the safety of concomitant aspirin (ASA) use are limited due to the small number of patients so exposed (ASA was allowed only in studies 21-91-201 and 21-96-202). Reportedly no clear evidence of interaction was found (as reported at the Advisory Committee meeting[53]). There is no data with which to estimate the effect on bleeding risk[54] produced by the concomitant administration of CLZ and clopidogrel (the antiplatelet agent recently approved for use in PAD patients).

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[53] I have requested the sponsor to submit the analysis presented there.
[54] or for that matter, the effect on mortality/morbidity produced by addition of CLZ to clopidogrel.

12.2.5   Common AE

The common ($\geq$ 1%) treatment-emergent AE that showed a statistically significant difference 0.05) between the 100 mg bid cilostazol group and the placebo group were: headache, diarrhea/abnormal stools, palpitation, tachycardia, arrhythmia, peripheral vascular disorder, dizziness, and eye disorder. Those that showed a dose-relationship were headache, diarrhea/abnormal stools, palpitation, and tachycardia.

12.2.6   Laboratory findings

Elevated mean BUN was, in the two highest dose CLZ groups, more prevalent than control. The occurrence of any degree of abnormally elevated serum creatinine was, in each drug group, more prevalent than control, and the relationship to dose was monotonic. There were no pooled CPK levels reported with which one could assess the possibility of myolysis contributing to the elevated creatinines. Hematology findings showing at least numerically greater mean prevalence of abnormality in one or another CLZ dose group (relative to placebo), but no monotonic relationship to dose, were low hematocrit, and low erythrocyte count. Low hemoglobin, leukopenia, and thrombocytosis also showed at least numerically greater mean prevalence of abnormality in one or another CLZ dose group, and also manifested an apparent[55] dose response.

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[55] the small size of the high dose sample precludes definitive statements about dose response.

13 CONCLUSIONS

13.1 Efficacy

The efficacy data submitted have adequately demonstrated the anti-claudication efficacy of CLZ at a dose of 200 mg/d, but there is not yet a convincing basis with which to conclude that CLZ is more efficacious than PTX in this regard.

13.2 Safety

The submitted safety data are adequate to describe the observed adverse morbidity profile of this drug, but that in the absence of an adequately powered, placebo-controlled survival trial there is inadequate precision in the present mortality estimate for one to confidently exclude a clinically important PDE III inhibition-based adverse survival effect in the claudication population studied.

Steven Mark Rodin, MD   7/27/98

Steven Mark Rodin, M.D.   Date
Medical Officer

cc: HFD-110/ division file, CSO, A. Karkowksy, ▇▇▇▇ and S.Rodin